Apgar score after induction of anesthesia for canine cesarean section with alfaxalone versus propofol

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Abstract: The effects of alfaxalone and propofol on neonatal vitality were studied in 22 bitches and 81 puppies after their use as anesthetic induction agents for emergency cesarean section. After assessment that surgery was indicated, bitches were randomly allocated to receive alfaxalone 1 to 2 mg/kg body weight or propofol 2 to 6 mg/kg body weight for anesthetic induction. Both drugs were administered intravenously to effect to allow endotracheal intubation, and anesthesia was maintained with isoflurane in oxygen. Neonatal vitality was assessed using a modified Apgar score that took into account heart rate, respiratory effort, reflex irritability, motility, and mucous membrane color (maximum score = 10); scores were assigned at 5, 15, and 60 minutes after delivery. Neither the number of puppies delivered nor the proportion of surviving puppies up to 3 months after delivery differed between groups. Anesthetic induction drug and time of scoring were associated with the Apgar score, but delivery time was not. Apgar scores in the alfaxalone group were greater than those in the propofol group at 5, 15, and 60 minutes after delivery; the overall estimated score difference between the groups was 3.3 (confidence interval 95%: 1.6-4.9; $P < 0.001$). In conclusion, both alfaxalone and propofol can be safely used for induction of anesthesia in bitches undergoing emergency cesarean section. Although puppy survival was similar after the use of these drugs, alfaxalone was associated with better neonatal vitality during the first 60 minutes after delivery.

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Apgar score after induction of anesthesia for canine cesarean section with alfaxalone versus propofol

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Abstract

Objective: To compare alfaxalone and propofol as anesthetic induction agents in dogs undergoing emergency cesarean section in respect to their clinical effects on neonatal vitality, assessed by performing an Apgar score. **Study design:** Randomized blinded clinical trial of 22 female dogs with their 81 puppies delivered by emergency cesarean section. **Methods:** After decision for emergency cesarean section was made, dogs were allocated randomly to one of two treatment groups for anesthetic induction: alfaxalone 1-2 mg/kg BW or propofol 2-6 mg/kg BW, both given intravenously to effect to allow endotracheal intubation. No premedication / sedatives were administered prior to delivery of the offspring. Anesthesia was maintained with isoflurane in oxygen, and fentanyl infusion was started following delivery of the last puppy. To assess vitality of neonatal puppies, an Apgar score including the parameters heart rate, respiratory effort, reflex irritability, motility and mucous membrane color was performed at 5, 15 and 60 min post-delivery for each puppy. **Results:** Total anesthesia duration and delivery time of puppies were comparable in both groups (P = 0.87 and P = 0.511). Puppies in group alfaxalone had significantly higher Apgar scores (median 7.0 [$Q_{0.1}$2.0;$Q_{0.9}$9.0], 9.0 [6.0;10.0] and 10.0 [9.0;10.0]) at all three evaluation time points (5, 15 and 60 min post-delivery, respectively) than puppies in group propofol (3.5 [1.7;7.0], 6.5 [2.0;10.0] and 9.6 [6.1;10.0], respectively). The estimated group effect was a difference of 3.3, CI 95 % (1.6;4.9) (P < 0.001). Neither the number of delivered puppies nor the proportion of surviving puppies 60 min post-delivery differed between the groups (P = 0.168 and P = 0.149, respectively). **Conclusions:** Induction of anesthesia with alfaxalone was associated with higher neonatal Apgar score. Both protocols can be safely used for induction of anesthesia in dogs undergoing emergency cesarean section.

Kommentar [..1]: Ev noch schreiben indicating better viability-oder so für nicht Reproduktionsmediziner

Keywords: neonatal dog; cesarean section; anesthesia; alfaxalone; propofol; Apgar score

1. Introduction

As about 16 % of all pregnant bitches suffer from dystocia when giving birth and more than 60 % of bitches with dystocia end up having a cesarean section (section), performing an emergency section is a routine procedure of paramount importance in small animal obstetrics [1,2]. Various anesthetic techniques have been proposed [2-5]. All anesthetic drugs, including inhalant anesthetic agents, cross the placenta and the blood-brain barrier of the fetus and lead therefore to neonatal depression, although to a variable extent [3-5]. The anesthetic protocol chosen should provide optimal maternal and fetal conditions, with minimal neurological and cardiorespiratory depression [4]. Both maternal lethargy and reduced neonatal vitality during the critical first postoperative hours result in reduced colostrum intake and increased mortality rate of the puppies [3,5-7]. Currently, many veterinary clinics and practices use an anesthetic protocol with propofol induction followed by isoflurane maintenance, with or without additional sedatives and / or analgesics. Usually, anesthetic depth is increased after delivery of the last puppy, and supplementary analgesics are administered [2,6-9].

Anesthetic induction with propofol iv followed by isoflurane maintenance was reported to result in improved puppy vigor and newborn survival rates compared to other general anesthetic protocols and was considered almost equal to epidural anesthesia [6-8]. Recovery from propofol is normally prompt and smooth due to rapid redistribution and metabolism, and although it crosses the placental barrier, it is rapidly cleared from the neonatal circulation [5,10,11].

The neuroactive steroidal combination Saffan (a mixture of alfaxalone and alfadolone solubilized in 20 % of a polyoxyethylated castor oil called Cremophor EL) was used widely in the 1970s, 80s and 90s in cats and was considered to be a very safe anesthetic agent for anesthesia induction and short procedures [12]. In dogs, its use was severely limited due to a Cremophor EL-induced histamine release and a subsequent fall in arterial blood pressure with urticaria and skin erythema, resulting in serious anaphylactoid reactions in this species [13]. However, after pre-anesthetic medication with an antihistaminic agent

(chlorpheniramine maleate), Bomzon et al. reported Saffan to be a safe and predictable anesthetic agent for dogs undergoing section, and to be superior to thiopental [14]. In the last decade, a new Cremophor EL-free formulation of alfaxalone (3±-hydroxy-5±-pregnane-11,20-dione), without alfadolone, has been developed for use in small animals and registered in Australia, New Zealand, South Africa and the UK (Alfaxan®, Vétoquinol, UK). The new formulation uses a cyclodextrin base (2-hydroxypropyl- β -cyclodextrin, HPCD) as solubilizing agent and does not cause histamine release [15,16]. Alfaxalone was shown to provide a rapid and smooth induction of anesthesia with rapid recovery of consciousness and minimal respiratory depression at clinical doses [16,17]. Alfaxalone has a wide margin of safety, a short total body clearance and harmonic mean plasma terminal half-life [16]. Although alfaxalone is nowadays routinely used for induction of anesthesia in dogs and cats in many countries, it has never been evaluated in regard to its efficacy for section. Therefore, the objective of this study was to evaluate, in a clinical setting, the effects of alfaxalone as anesthetic induction agent for dogs undergoing emergency section on neonatal vitality and compare them to those of propofol.

2. Material and methods

2.1. Animals

A series of 22 client-owned bitches with their total of 81 puppies delivered by section were included. Age of the bitches ranged between one and 11 years (3.0 [1.3;6.2]). Their body weight was between 1.6 and 51 kg BW (7.3 [2.1;28.4]). Section was indicated due to dystocia in all cases. Indications were: poor general conditions of the dam, birth canal obstructions, fetomaternal disproportion, faulty fetal position, fetal heart rate of one or more puppies less than 180 bpm over several minutes, dystocia with more than two

puppies remaining to deliver as well as unsuccessful medical management of dystocia [18]. The local ethics committee approved the study.

2.2. Anesthetic protocol

All dams were started on intravenous fluids immediately after presentation (Lactated Ringer's solution at an infusion rate of 10 to 20 mL/kg BW/h; in case of poor general condition or severe dehydration, HAES (HAES-steril 10%, Fresenius Kabi, Germany) at an infusion rate of 1 to 2 mL/kg BW/h was added). Infusion was maintained until the patient had fully recovered from anesthesia. Before induction of anesthesia, patients were pre-oxygenated for 5 min using flow-by oxygen (L/min). All patients received a single intravenous administration of cefazolin (Kefzol®, Teva Pharma, Switzerland) at a dosage of 20 mg/kg BW. Neither sedatives nor analgesics were administered. For anesthesia induction, the 22 dogs were randomly assigned to one of two groups: group Al received alfaxalone (Alfaxan®, Vétoquinol, UK) at a dosage of 1 to 2 mg/kg BW (given to effect) and group Pr propofol (Propofol 1% MCT, Fresenius Kabi, Germany) at a dosage of 2 to 6 mg/kg BW (given to effect) iv. All anesthetists participating in the study were experienced. After intubation, anesthesia was maintained with isoflurane (Isoflo®, Abbott, Dr. E. Graeub AG, Switzerland) in oxygen at the dosage to effect. Surgery was performed by one of five experienced surgeons. Both the surgeons and the one observer performing post-anesthetic evaluations (first author) were blinded in regard to the induction agent used. Immediately after delivery of the last puppy, a continuous rate infusion of fentanyl (Fentanyl, Sintetica SA, Switzerland) at a dosage of 5 mcg/kg BW/h was started and stopped at the end of surgery. Twenty min before the end of surgical procedure, all patients received both buprenorphine (Temgesic®, Reckitt Benckiser, Switzerland) at a dosage of 14 mcg/kg BW and carprofen (Rimadyl®, Pfizer AG, Switzerland) at a dosage of 4 mg/kg BW iv. During the surgical procedure, the following time points were recorded:

130 administration of anesthesia induction agent, delivery of last puppy and end of isoflurane
131 administration. Total duration of anesthesia was defined as time from anesthetic induction
132 until stop of isoflurane inhalation. Delivery time of puppies was defined as time from
133 anesthetic induction until delivery of the last puppy.

134

135 2.3. Resuscitation of the neonates

136

137 Immediately after delivery, each puppy had fluid cleared from the upper airways by
138 suctioning and was rubbed and blow-dried on warm beddings. All puppies were
139 oxygenated using flow-by oxygen (L/min), and, if breathing did not immediately start,
140 gentle mouth-to-nose breathing was initiated in order to expand the neonate's lung. If
141 breathing still was inadequate, a centrally acting analeptic was administered (Respirot®,
142 Novartis Tiergesundheit AG, Switzerland), at a dosage of one to two drops per puppy
143 applied buccally. Each puppy received a single subcutaneous bolus of glucose 5 % (3 to 5
144 mL/100 g BW). Resuscitation was performed for at least 30 min if a heartbeat was
145 detected. The umbilical cords were ligated in 0.5 to 1 cm distance to the abdominal wall
146 and the stalks disinfected with a weak iodine solution (Betadine®, Mundipharma,
147 Switzerland). Each puppy had its weight recorded and a detailed clinical examination has
148 been performed. After stabilization, puppies were transferred to a newborn incubator (for
149 detailed description see Michel and Reichler 2008 [2]).

150

151 2.4. Assessment of neonatal puppies

152

153 In order to objectively assess neonatal vitality, we used the modified Apgar score for
154 puppies formulated by Veronesi et al. [9], including the following parameters: heart rate,

respiratory effort (respiratory rate and type of crying), reflex irritability, motility and mucous membrane color. Each parameter was rated as 0 (absent), 1 (detectable, weak) or 2 (detectable, strong). The sum of all parameters, up to a maximum of ten, provided the total Apgar score, which was recorded for each individual puppy at 5, 15 and 60 min post-delivery.

2.5. Statistical Analysis

Microsoft Office Excel 2007 was used to record data. Statistical analysis was performed using Stat View 5.0® (SAS Institute Inc., Cary, NC, USA). Linear mixed models were performed with R (Team 2010) and the packages nlme [19]. Graphs were performed with Prism 4.0b (GraphPad Software, CA, USA). All the continuous variables were summarized by descriptive statistics as median values with the 10^{th} and 90^{th} percentiles in parenthesis ($Q_{0.1}$, $Q_{0.9}$), and box plots. Mann-Whitney U-tests were performed to assess if the groups AI and Pr differed significantly pre-operatively (age, body weight, maternal body temperature, heart rate, respiratory rate, PCV) and intra- and / or postoperatively (body temperature, heart rate, respiratory rate, blood pressure, total duration of anesthesia, delivery time of puppies, litter size). Chi-square tests were used to assess if the two groups differed significantly with regard to the proportion of bitches with or without ovariohysterectomy, parity and the proportion of life and dead puppies. Linear mixed models, accounting for clustering within puppy and bitch, were performed to assess if pre- and intraoperative factors (group AI, Pr and delivery time of puppies) were significantly associated with the Apgar score. Model selection (e.g. deciding which of the explanatory variables should be included in the final model) was based on the Akaike information criteria (AIC). Model validation was based on checking the residuals visually for homogeneity and independence. The results with $P < 0.05$ are considered to be significant.

3. Results

A total of 22 litters with their 81 puppies born via section were included. Group Al and Pr were assigned 11 bitches each. The bitches of both groups were comparable regarding their breed affiliation. The groups did not differ at admission in respect to age (P = 0.718), parity (P = 0.47), pre-anesthetic body weight (P = 0.818), body temperature (P = 0.953), heart rate (P = 0.224), respiratory rate (P = 0.773) and PCV (P = 0.97) at admission. Body temperature, heart rate, and mean blood pressure did not differ intraoperatively between both groups (P = 0.885, P = 0.496 and P = 0.103, respectively). Total anesthesia duration was comparable in both groups (group Al: 98.0 [54.6;117.0] min; group Pr: 90.0 [67.8;126.0] min; P = 0.87). Delivery time of puppies ranged between 10-55 (24.0 [13.5;37.5]) min and did not differ significantly between the groups (P = 0.511). Litter size ranged from one to 10 puppies (4.5 [2.0;7.6]); with a median of 3.0 [1.0;7.0] puppies born after section and did not differ between the two groups (P = 0.2 and P = 0.168, respectively). The birth weights were between 71 to 524 g and within the normal range for each breed. Five bitches of group Al and six bitches of group Pr were ovariohysterectomized on owners request after section (P = 0.67). The maternal recovery was uneventful, smooth and rapid in both groups.

A total of 81 puppies were born via section. Two of the 73 puppies that were born alive died within the first 60 min after birth. Table 1 shows the number of dead and live puppies delivered and death and survival 1 h after parturition via section listed by the type of anesthetic induction. Neither the number of delivered puppies nor the proportion of surviving puppies 60 min post-delivery differed between the groups (P = 0.168 and P = 0.149). According to the best model, group (choice of anesthetic induction with alfaxalone or propofol) and evaluation time of Apgar score but not delivery time of puppies were significantly associated with the Apgar score (P < 0.001, P < 0.001 and P = 0.625,

209 respectively): Figure 1 shows that at all three assessment points (5, 15 and 60 min post-
210 delivery), the Apgar scores of puppies in group AI were significantly higher than those of
211 puppies in group Pr. The estimated difference between both groups was 3.3, CI 95 %
212 (1.6;4.9). Over time the Apgar score increased in both groups: 5 min post-delivery, 68 %
213 of the 41 puppies in group AI had a high (7 to 10), 15 % a medium (4 to 6) and 17 % a low
214 (0 to 3) Apgar score. In group Pr, 19 % of the 32 puppies had a high, 31 % a medium and
215 50 % a low Apgar score.

216

217 **4. Discussion**

218

219 The present study demonstrated that alfaxalone is suitable for anesthesia induction in
220 dogs undergoing section. As it resulted in significantly improved neonatal Apgar scores
221 compared to propofol its use might be even superior to the currently used standard
222 anesthetic. Following alfaxalone neonates were earlier fit enough, what may increase the
223 uptake of colostrum in the first postoperative hours.

Kommentar [..2]: To do what?

224 Use of the Apgar scoring system adapted for puppies by Veronesi et al. [9] and
225 performing the scores not only at 5, but also at 15 and 60 min post-delivery proved to be
226 very suitable for assessing neonatal vitality and particularly individual improvement, and
227 allowed for objective comparison between the anesthetic protocols. Several recent studies
228 have examined the association between Apgar score and short-term survival prognosis,
229 umbilical vein lactate measurement, blood gas assessment and acid base changes in
230 neonatal dogs [9,20-22]. Groppetti et al. found that Apgar scores and umbilical lactate
231 concentration at birth, an important marker of fetal and neonatal distress, were
232 significantly correlated in puppies [22]. The value of the Apgar score in predicting short-
233 term survival is less clear. Whereas one group reported a significant correlation between
234 moderate to low Apgar scores and the percentage of puppies death shortly after birth,

another group could not confirm this finding [9,22]. Section has a significant impact on Apgar scores: Groppetti et al. observed low viability and poor Apgar scores in 100 % of puppies born from emergency section and in 92 % of puppies born from elective section, but only in 30 % of puppies delivered vaginally [22]. Although in their study propofol was used as induction agent, in our study the neonatal vitality after section was superior, not only in group Al but also in group Pr: only 17 % and 50 % of puppies were considered to have poor Apgar scores at 5 min after delivery, respectively. In agreement with the findings in previous studies, the Apgar scores in our study improved considerably in the first 60 min post-delivery [20,21].

The puppy survival proportion in our study (91 % at birth, 88 % after the first hour post delivery) was comparable to other authors. Moon et al. reported 92 % at birth and 87 % at birth and first two hours, Funkquist et al. 74 % at birth and 71 % at birth and first 20 min, and Moon-Massat and Erb 81 % at birth [6-8]. Luna et al reported an exceptionally low mortality rate of 4 % of puppies born dead following a section [4].

Unfortunately we were not able to retrospectively decide for how long the bitch had been in labor until surgery was performed, due to vague owner information. Total length of parturition is the most important parameter determining neonatal viability and vitality, and prolonged parturition time is negatively associated with neonatal survival [22,23]. Though, as dogs in group Al and Pr did not differ significantly in any clinical and hematological parameters examined on presentation, we consider the groups comparable. Further limitations were small sample size and the clinical setting with dogs of different breeds, parity and pre-anesthetic treatments included. These limitations, however, are also strength of the present study, because we were able to evaluate the effects of propofol and alfaxalone under realistic clinical conditions.

The most critical moments in a puppy's life are the time interval between delivery and first breath and first contact to and acceptance by the dam. Both the neonate's ability to breathe and the dam's ability to take care of her offspring are significantly influenced by

the anesthetic protocol chosen to perform a section [3,5,24]. Anesthesia during section can be divided in two stages: during the first stage, the fetuses are dependent on maternal cardiovascular system and during the second stage, after delivery of the last puppy, only the dam is exposed to anesthetic agents. Various anesthetic protocols have been described (for assessment of various anesthetic agents in regard to their suitability for section anesthesia (see Pascoe and Moon 2001, Michel and Reichler 2008 [2,3]). Although induction with propofol followed by isoflurane maintenance is considered to be superior to other general anesthetic protocols and equal to epidural anesthesia [3,6-8](Moon, Erb et al. 2000; Pascoe and Moon 2001; Moon-Massat and Erb 2002; Funkquist 1997), in individual cases other protocols may be preferable due to a practitioner's experience with a certain protocol or in order to minimize cardiorespiratory depression in critical patients [2,3,24]. Currently, the following anesthetic protocols are recommended as alternative: premedication with opioids followed by epidural anesthesia, with or without induction of general anesthesia (light plane), and maintenance with isoflurane [4,7] or anesthetic induction with etomidate, with or without additional opioids [3,4,7].

Propofol and alfaxalone are short acting hypnotic agents and provide short anesthesia induction and recovery from anesthesia. Both agents cross, as all centrally acting anesthetic agents, the placental barrier, which makes them comparable [5,25]. Alfaxalone has hypnotic, muscle relaxant and limited antinociceptive effects due to its interaction with the $GABA_A$ receptor of neurons and GABA neurotransmission enhancement [26]. Alfaxalone induces a dose dependent decrease in blood pressure, caused by peripheral vasodilation [17]. In clinically effective dosages, alfaxalone does not impair stroke volume ratio SVR [17,25]. Propofol also enhances GABA neurotransmission and it has no analgetic effect [27]. Compared with alfaxalone, propofol is reported to cause more cardiorespiratory depression and to increase $PaCO_2$ [17,25]. This may have influenced puppy vitality as alfaxalone and propofol have otherwise comparable values, i.e. for total body clearance [16].

Recovery of the dams in our study was smooth and rapid with both anesthetic agents, in agreement with the findings in previous studies [25]. Jiménez et al. have described poorer recovery quality when anesthesia was induced with alfaxalone rather than propofol [28]. However, results may be influenced by the fact that all dogs in their study suffered from a neurological condition, which may have altered response to different agents [28]. A further advantage of alfaxalone for practitioners is its longer shelf life and its higher resistance against microbial growth compared to propofol [29].

Performing a similar study, but including only elective sections would be an effective possibility to eliminate the influence of duration of labor on puppy survival. Also, question is raised as to which extent the induction-delivery-time may have an impact on the Apgar score. While some clinicians argue that the induction-delivery-time should be longer than the elimination half-life of the induction agent, therefore enabling its degradation by maternal metabolism rather than fetal, current data seems to challenge this hypothesis: neither longer induction-delivery-times improved puppy survival [8] nor a relationship between delivery time and Apgar score was obvious in the presented data.

5. Conclusions

We conclude that anesthetic induction with alfaxalone for dogs undergoing emergency section is equal or even superior to anesthetic induction with propofol, when followed by isoflurane maintenance. Clinically relevant is the fact that with alfaxalone, puppies have significantly higher Apgar scores at 5, 15 and 60 min post-delivery than with propofol. Especially in a clinical setting, when number of puppies often exceeds number of staff able to assist in reanimation, this can be advantageous.

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Table 1

Puppy death and survival at birth and 60 min after delivery according to the type of anesthetic induction for section.

Figure 1

407 Apgar scores from puppies of group AI and Pr at 5, 15 and 60 min after delivery.

408